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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,122	02/27/2004	Simon Benita	14945.0001	4640

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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/787,122	BENITA ET AL.	
	Examiner	Art Unit	
	Aradhana Sasan	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/06/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Amendments to claims filed 04/07/2004 are acknowledged.

2. Claims 1-15 are being presented for examination.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 10/06/2004 was filed. The submission is in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statement. See attached copy of PTO-1449.

Specification

5. The disclosure is objected to because of the following informalities: on page 1, line 16, "fourth" is misspelled as "forth", on page 6, line 22, "taken up" is misspelled as "uptake", on page 7, line 16, "free NH_2 groups" is mistyped as "NH_2 free groups", on page 9, line 19, "obtain" is misspelled as "obtained", and on page 29, line 4, "washes" is misspelled as "washed".

Appropriate correction is required.

Claim Objections

6. Claim 4 is objected to because of the following informalities: "free NH_2 groups" is misspelled as "NH_2 free groups". Appropriate correction is required.

7. Claim 11 is objected to because of the following informalities: "AMB8LK" is misspelled as "ANB8LK". Appropriate correction is required.

Drawings

8. It is recommended that the heading "Brief Description of Drawings" precede the description of the drawings.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific "compound presenting free NH_2 groups" (e.g. C_{10}-C_{24} alkylamine) and a specific "antibody" (e.g. AMB8LK), does not reasonably provide enablement for all compounds with free NH_2 groups and all antibodies.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The scope of the claim is broad enough to encompass the use of any compounds with free NH_2 groups (not just the use of cationic lipids such as stearylamine or oleylamine) and any antibodies (not just AMB8LK).

The specification discloses a "compound presenting free NH_2 groups is stearylamine or oleylamine" (page 7, lines 15-17) and "the AMB8LK antibody" (page 8, lines 24-26).

The working example provided is directed toward stearylamine (page 14, line 14 example 1) and AMB8LK F(ab)2 fragments (page 16, lines 14-16).

The specification does not teach that any compounds with free NH_2 groups and any antibodies can be used in the invention. The nature of the compound is such that the compound is linked to an antibody by a linker. Not all compounds with free NH_2 groups and not all antibodies would have this property.

The nature of the invention is a cationic emulsion comprising a compound with free NH_2 groups and an antibody and a method of producing the emulsion. The compound is linked to the antibody by a linker. The emulsion contains an active drug and the antibody targets antigens.

The state of the prior art teaches that stearylamine and oleylamine are cationic lipids that are used to confer positive charges on emulsions (Yang et al., Drug Development Research, page 477) and anti-ferritin monoclonal antibodies used for treating cancer (Kadouche et al. US 2002/0106324 used since WO 01/52889 translation was not provided).

Undue experimentation would be required to use the invention because it is not clear which compound with free NH_2 groups and which antibody is going to be used in the invention. In order to use any compound with free NH_2 groups and any antibody in the invention, the quantity of experimentation would be too great.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim. It would require undue experimentation to use the invention based on the breadth of this claim.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 14-15 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "with the other products necessary" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-2, 7-11 rejected under 35 U.S.C. 102(b) as being anticipated by Kadouche et al. (WO 01/52889).

Please note that Kadouche et al. (WO 01/52889) has a WIPO publication date of 07/26/2001. Since the English translation was not available, the corresponding US patent application publication (US 2002/0106324 A1) is being used in this instant rejection as a reference for the convenience.

The claimed invention is a cationic oil in water emulsion comprising a compound with free NH_2 groups and an antibody and a method for producing the emulsion. The compound is linked to the antibody by a heterobifunctional linker. The emulsion contains an active drug. The antibody (polyclonal or monoclonal) targets antigens.

Kadouche et al. (US 2002/0106324 A1) teaches a monoclonal antibody coupled to a cationic emulsion and also a cationic lipid (Page 5, [0064]). Kadouche teaches native antibodies as immune effectors used in anti-tumoral therapies, which involves "blocking a receptor of the target cell or an anti-idiotypic vaccination for the tumoral antigen" (Page 2, [0018]). Also taught are polyclonal antibodies along with their affinity for ferritins (Page 3, [0047] and Page 4, Table 1). Kadouche teaches an anti-ferritin monoclonal antibody and specifically AMB8LK which was "used to carry out a sandwich ELISA test to detect human ferritins" (Page 7, [0114]).

Kadouche anticipates instant claim 2 since this reference teaches a cationic emulsion and a positive zeta charge is an inherent feature of a positive or cationic emulsion.

The claim limitations of polyclonal and monoclonal antibodies, antibody targeting an antigen (H-ferritin), and AMB8LK as the antibody are anticipated by Kadouche.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 3-6, 12-15 rejected under 35 U.S.C. 103(a) as being unpatentable over Kadouche et al. (WO 01/52889), in view of Yang et al. (Drug Development Research, 2000), and further in view of Kirpotin et al. (Biochemistry, 1997).

The teaching of Kadouche is stated above. Kadouche does not specifically teach stearylamine or oleylamine as the cationic lipids or a linker chosen from N-1 stearyl-maleimide (SM), oleylmaleimide, succunimidyl trans-4-(maleimidylmethyl)cyclohexane-l-carboxylate (SMCC) and succinimidyl 3-(2-pyridyldithio)propionate (SPDP).

Yang et al. (Drug Development Research, 2000) teach cationic oil in water emulsions where the internal core of the emulsion is used as a carrier of lipophilic drugs (Page 476, Col. 1). The emulsion formulation is based on cationic surfactants, which include stearylamine and oleylamine (Page 477, Col. 1 and Col. 2). Yang also teaches that the "positive charge of submicron emulsions results from cationic lipids, ... and

surfactants, such as stearylamine, ... oleylamine" (Page 478, Col. 1). Furthermore, Yang teaches, "an emulsion is stabilized by the addition of emulsifying agents which lower the interfacial tension and form a film at the oil–water interface, which acts as a mechanical barrier to droplet coalescence ... The electrical surface charge of droplets is produced by the composition of interfacial film-forming components" (Page 479, Col. 1).

A person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the teaching of Kadouche (antibody coupled to a cationic emulsion) with the cationic lipids taught by Yang. The motivation to combine these references is provided by the statement: "intravenous emulsions are considered excellent carriers for lipophilic drugs, which are often difficult to deliver. They are biodegradable, biocompatible, physically stable, and relatively easy to produce on a large scale" (Yang, Page 476). Moreover, "advantages of positively charged emulsions include enhancing electrostatic interactions with the negatively charged moieties of the cell membranes in numerous accessible organs" (Yang, Page 484, Col. 1). Emulsion preparation method is also taught by Yang.

Regarding instant claim 12, Kirpotin (Biochemistry, 1997) teaches antibody based targeting of drugs to cancer cells and specifically used maleimide-terminated spacers (Abstract). Among the materials used was N-succinimidyl-4-(N'-maleimidomethyl)-cyclohexane-1-carboxylate, which is one of the heterobifunctional linkers in instant claim 12.

A person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the teaching of Kadouche (antibody coupled to a

cationic emulsion) and the teaching of Yang (cationic lipids) and further use the maleimide linker taught by Kirpotin. The motivation to combine is provided by the "stability of the maleimide function" which was "sufficient to ensure quantitative conjugation of Fab' fragments bearing reactive free thiols..." (Page 73, Col. 1).

Conclusion

1. No claims are allowed.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AS. VICKIE KIM
PRIMARY EXAMINER